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findings. If the podocytes are the primary excreters of IL-18, where are the activated Th1 cells? What is the stimulus for production and secretion of IL-18? Are the podocytes and other renal cells perhaps endocytosing IL-18 rather than producing it? Alternatively, we must ask whether IL-18 production by these cells is instead a consequence rather than an initiator of neutrophil activation. As we know that proteinase 3 is capable of activating pro-IL-18 *in vitro*, what are the functional consequences of this in proteinase 3-ANCA disease? It would be expected that any cytokine secreted by podocytes would pass into the urine rather than cross the glomerular basement membrane opposite to the normal direction of filtration; direct secretion by the podocytes into the vasculature would truly be a novel finding. Regardless, this report reveals that podocytes may be direct participators in the immune dysfunction of ANCA disease, and that IL-18 may be responsible for neutrophil priming *in vivo*.

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Fibroblast growth factor 23: the making of a hormone

SC Schiavi[1]

Fibroblast growth factor 23 (FGF23) modulates serum phosphate and 1α,25-dihydroxyvitamin D3 levels. FGF23 expression is in turn regulated by 1α,25-dihydroxyvitamin D3 and dietary phosphate load, and is strikingly elevated during renal progression. In this issue, Nagano and colleagues report that FGF23 can be modulated by intermittently high dietary phosphate in the presence of compromised renal function.

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Over the past several years, accumulating evidence has documented the role of fibroblast growth factor 23 (FGF23) in the control of phosphate and vitamin D homeostasis. These data show that FGF23 acts in accordance with the definition of a hormone: a circulating protein that targets specific tissues distant from its site of production. FGF23 acts directly on the kidney to regulate the synthesis of 1α,25-dihydroxyvitamin D_3 and the surface expression of the sodium phosphate transporters NaPi-IIa and -IIc.[1–4] Several reports now demonstrate that serum FGF23 concentrations increase both in response to dietary phosphate load with normal renal function and in response to increasing serum phosphate levels associated with progressive renal failure.[1,3] Despite this body of data, a debate continues regarding the physiological relevance of FGF23 as a major regulator of phosphate homeostasis. In particular, it has been argued that elevated FGF23 in renal disease is a consequence of reduced renal clearance and therefore may not play a direct role in the progression of renal disease and its associated complications.

The study presented in this issue by Nagano *et al.*[5] represents an important advancement beyond the previously identified association of elevated FGF23, phosphate, and parathyroid hormone (PTH) levels in renal disease.[1,3,4] By using a model of severe chronic kidney disease and including an experimental arm in which phosphate levels were regulated by intermittent dosing of the phosphate binder sevelamer hydrochloride, the authors have provided convincing evidence that FGF23 serum concentrations were influenced by elevated dietary and serum phosphate. Importantly, the data argue that decreased renal function cannot adequately explain the dramatic rise in FGF23 serum concentrations associated with renal insufficiency, as changes in serum FGF23 levels were observed in the presence of severely compromised kidney function. Together with the substantial data demonstrating direct actions of FGF23 on renal phosphate excretion, these results imply that the levels of FGF23, like those of PTH, may rise in response to the increasing pressure to excrete phosphate.

The study by Nagano *et al.*[5] also demonstrates another important feature of FGF23 regulation: that FGF23 serum levels are modified rather slowly in response to increased dietary phosphate. Although changes in serum phosphate and PTH occurred 1 day after sevelamer treatment or removal, there was an additional lag before FGF23 levels were altered. The mechanism triggering the slow regulation of FGF23 is not clear, but the delay suggests that phosphate does not directly control FGF23 synthesis. This result implies that FGF23's function is most important as a chronic rather than an acute response to changes in phosphate and partially explains the need for

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two phosphate-regulating hormones. Such an argument makes further sense when one considers the opposing actions of FGF23 and PTH in the regulation of 1α,25-dihydroxyvitamin D_3 synthesis. PTH classically induces synthesis of 1α-hydroxylase, whereas FGF23 inhibits its synthesis.[1,4] Thus, it has been proposed that FGF23 counterbalances the actions of PTH by keeping a tighter rein on vitamin D and serum calcium levels in the face of sustained phosphate challenges.[6]

The working hypothesis (Figure 1) incorporates the known actions of FGF23, and the finding that FGF23 elevation in response to increased phosphate is delayed relative to PTH, into the accepted dogma defining the mechanisms of mineral homeostasis. In this model, (1) increased dietary phosphate uptake results in a rise in serum phosphate concentrations and subsequent increased PTH secretion from the parathyroid gland. (2) PTH induces phosphate excretion by downregulating the renal sodium phosphate transporter NaPi-IIa. (3) Simultaneously, PTH induces synthesis of 1α,25-dihydroxyvitamin D_3 by upregulating 1α-hydroxylase. (4) 1α,25-Dihydroxyvitamin D_3 promotes a rise in serum calcium by increasing intestinal calcium absorption, calcium and phosphate release from bone, and calcium reabsorption in the kidney. (5) FGF23 synthesis in bone cells is also induced by increased production of 1α,25-dihydroxyvitamin D_3, whereas (6) PTH synthesis is inhibited by rising calcium levels. (7) Increased production of FGF23 sustains the dampened renal phosphate reabsorption while (8) preventing the unchecked induction of 1α,25-dihydroxyvitamin D_3 synthesis and calcium mobilization.

The above model should be approached not simply from a phosphate-centric viewpoint but rather as a homeostatic pathway necessary for maintenance of both calcium and phosphate. Thus, according to the proposed paradigm, PTH actions would predominate when phosphate levels were high and calcium levels were low, whereas FGF23 actions would predominate when both phosphate and calcium levels were high. This hypothesis would further suggest a currently unreported role for elevated calcium in the regulation of FGF23.

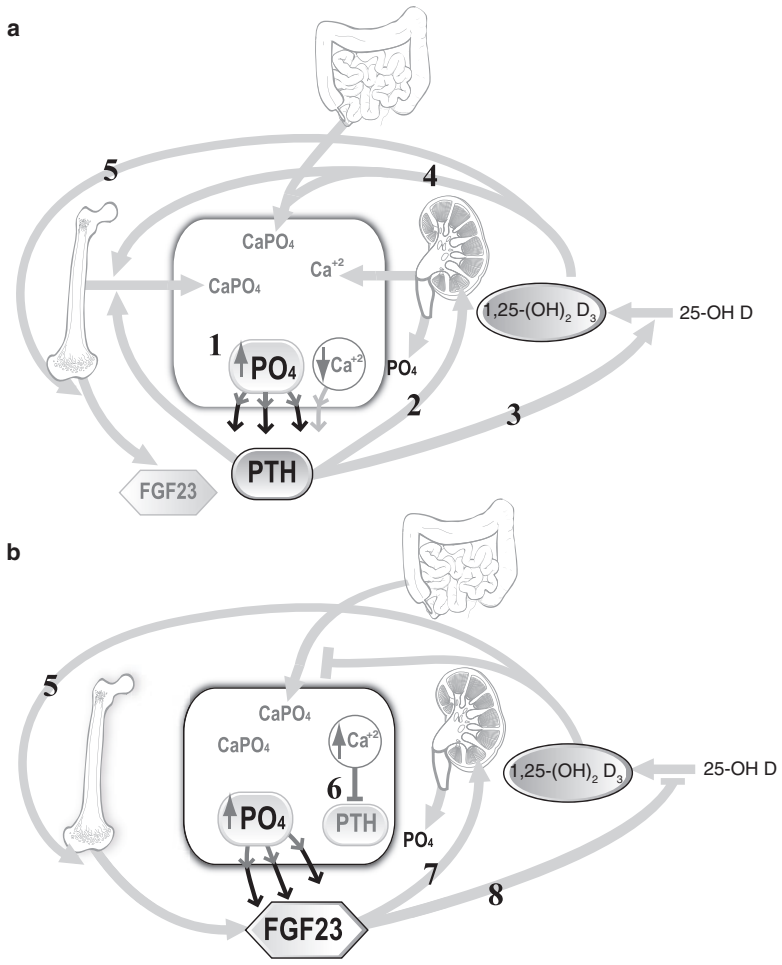

Figure 1 | Model depicting potential role of FGF23 in mineral homeostasis. (a) PTH actions initiate control of phosphate and calcium balance. (b) FGF23's proposed function to counterbalance PTH regulation of vitamin D.

If FGF23 is important for normal regulation of mineral homeostasis, then dysregulation of this hormone should have pathological consequences. Indeed, overexpression of FGF23 in the presence of a functioning kidney in humans and animal models results in hypophosphatemia, rickets, and osteomalacia.[1,2] In renal disease, declining vitamin D production and increased PTH secretion due to hyperparathyroidism contribute to renal osteodystrophy and vascular calcification. FGF23 may indirectly contribute to these processes through its regulation of vitamin D and PTH. FGF23's inhibitory action on 1α-hydroxlyase, and the inverse relationship between FGF23 and declining 1α,25-dihydroxyvitamin D_3, are consistent with the hypothesis that FGF23 contributes to the progressive decrease in vitamin D commonly associated with chronic renal insufficiency. Furthermore, a recent study used multiple linear regressions and concluded that increased FGF23 levels occur early in chronic kidney disease, before the development of serum mineral abnormalities, and are independently associated with serum phosphate, fractional excretion of phosphate, and calcitriol deficiency.[7]

Although *in vivo* administration of FGF23 does not acutely promote PTH secretion, secondary hyperparathyroidism is generally associated with chronic FGF23 elevation in individuals with chronic renal insufficiency and in animal models with sustained elevated FGF23.[1,3,7] Furthermore, circulating FGF23 levels, rather than PTH levels, are most predictive of refractory hyperparathyroidism. The cumulative data currently suggest that FGF23 may

contribute to hyperparathyroidism indirectly by downregulating 1α,25-dihydroxyvitamin D_3, with the subsequent decrease in serum calcium enhancing PTH production.

It is unknown whether high FGF23 levels contribute to altered bone and vascular health during renal disease. Physiological levels of circulating FGF23 may in fact be protective against ectopic calcifications and vascular disease.[8] In mice, *FGF23* gene ablation results in soft tissue calcifications. Human FGF23 mutations that reduce functional levels of FGF23 protein cause tumoral calcinosis, a disease associated with severe ectopic calcifications.[1] Thus, there is currently no evidence suggesting that elevated FGF23 has a direct impact on vascular calcification.

Alternatively, FGF23 may play a role in renal osteodystrophy. Although a direct action of FGF23 on bone has not been rigorously demonstrated, cells of the osteoblast lineage produce FGF23, and high FGF23 levels are associated with osteomalacia. The possibility that FGF23 may directly control bone mineralization is consistent with an intriguing hypothesis that FGF23 coordinates renal phosphate handling to meet the needs of mineralization.[9] Additional studies will be needed to clarify such a putative role for FGF23 as a general regulator or sensor of bone mineralization, and how its subsequent dysregulation may contribute to mineralization defects associated with chronic kidney disease.

One critical piece of information that is still lacking is whether all of the FGF23 measured in serum from individuals with renal disease is biologically active. Taking our lessons from experiences with the measurement of PTH, the existing enzyme-linked immunosorbent assays may not detect or distinguish all relevant forms of FGF23 in circulation. It remains to be determined whether fragments of FGF23 exist with altered or inhibitory functions that either interfere with or remain undetected by the current assays.

Merely 5 years have passed since FGF23 mutations were linked to phosphate dysregulation.[10] The intervening time has brought rapid advances in the understanding of FGF23 function, and with them a decline in the skepticism over the existence of yet another hormone controlling mineral homeostasis. Although questions remain, studies such as those presented by Nagano and colleagues[5] bring us closer to a more complete understanding of mineral metabolism, allowing us to consider the effects of FGF23 alongside those of more traditional hormones. Move over, PTH and vitamin D — another hormone has arrived!

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